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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,147	PRESTA ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *23 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4-7 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) *1,4-7 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 23, 2006 is acknowledged and has been entered. Claims 1 and 23 have been amended. An action on the RCE follows.

2 Claims 1, 4-7, 23 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC 112

4. Claims 1, 4-7, 23 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the paper mailed October 18, 2005, Section 5, pages 2-9, mailed March 28, 2005, Section 5, pages 2-8.

Applicant reiterates arguments drawn to dosage determination. The arguments were previously considered and were not found persuasive for the reasons of record. Further, although Applicant states that one would know how to increase an applied dose if it happens that there is indeed sequestration of antibody, however, Examiner once again notes that no nexus has been established between the claimed method and treatment of epilepsy.

Applicant argues that the Examiner has presented no data demonstrating that a sequestration effect might be expected *in vivo*. The argument has been considered but has not been found persuasive because the art recognizes the presence of non-productive receptors and splice variants of trkC for the reasons of record. Further, the specification clearly teaches the similarity of the structures of

trk receptors on page 2 and Du et al (World J. Gastroenterol, 2003, 9(7):1431-1434) teaches that the structure of the three trk receptors consists of cellular external region, transcellular membrane region and cellular internal region. The receptors all are tyrosine kinases, and there is 66-68 % of homology between them (p. 1433, col 1). In addition, Roitt et al (Immunology, 1993, Mosby, St. Louis, p 6.4-6.5) teach that when the determinants of antigen A are shared by another antigen, B, then antibodies that bind to those determinants in A will also react with B and that this phenomenon is termed cross-reactivity (see Fig 6.8 on page 6.4 and p. 6.5, para 1). Given the degree of identity between the trk receptors, given that the broadly claimed antibodies would be expected to cross react with other forms of trk, due to the structural and sequence homologies of the receptors, given that the specification further teaches that there are two known forms of trkA, three known forms of trkB, and at least four forms of trkC (again p. 2 and Figure 1) which one skill would expect to also share significant homology with SEQ ID NO:6, anyone of skill would immediately realize that cross reactivity of the antibody would be expected to be a major problem for therapy. In addition, Du et al further teach that trk receptors have been found in non-neural tissues, thus expanding the sites wherein the antibody may be absorbed. In addition, the biological stability, half-life or clearance from the blood of the claimed therapeutic are important parameters in achieving successful therapy. The antibody may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the antibody In addition, the antibody may not otherwise reach the target because of its inability to penetrate tissues, the blood brain barrier, or cells where its activity is to be exerted, would be expected to be absorbed by fluids, cells and tissues where

antibody has no effect upon epilepsy, circulation into the target area may be insufficient to carry the antibody and a large enough local concentration may not be established. Once again, the specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predictably use the claimed invention with a reasonable expectation of success.

Applicant reiterates arguments drawn to the nexus of NT-3, neuronal sprouting and trkC. The arguments have been considered but have not been found persuasive for the reasons of record. Further, it is noted that a search of the literature, today, twelve years post filing did not reveal a single reference wherein a predictable nexus between NT-3, neuronal sprouting, trkC and treatment of epilepsy has been established.

Applicant argues that the claims are explicitly directed to treating aberrant neuronal sprouting in epilepsy and that the specification explicitly discloses that the invention is useful in treating epilepsy. The argument has been considered but has not been found persuasive as the specification does not explicitly disclose that the invention is useful in treating epilepsy, but rather states on page 68 that "it is believed" (the claimed method) "to be useful in the treatment of pathological conditions associated with endogenous neurotrophin production such as ..... epilepsy". It appears that this is the belief of the inventors of the instant application. However, for the reasons of record, this belief is not enabled.

Applicant argues that at the time the invention was made, it was recognized in the art that aberrant sprouting might be affected by neurotrophin levels and neurotrophin receptor activity. Further, Applicant argues that given the disclosures

in the specification, that the nexus between inhibition of the trkC receptor and epilepsy treatment would instantly be appreciated by one skill. The argument has been considered but has not been found persuasive because, for the reasons of record, the art clearly did not recognize a predictable nexus between trkC and treatment of epilepsy.

Applicant argues that the Hongo Declaration further demonstrates the activity of the antibodies of the claims and provides corroboration of the utility of the claimed invention. The argument has been considered but has not been found persuasive because the issue is not that the claimed invention lacks utility, but rather that the specification as originally filed does not enable the claimed invention. Further, the data presented in the Hongo Declaration is not commensurate in scope with the claimed invention drawn to *in vivo* therapy. The Hongo declaration is drawn to *in vitro* assays of binding of monoclonal antibodies, which are apparently specific to trkA and trkC, well as the effects of these monoclonal antibodies on the activity of receptors that were transfected into CHO cell lines. Apparently, in view of the results of these *in vitro* assays, Dr. Hongo opines that molecules that antagonize trk activity find use in the treatment of diseases characterized by trk expression. However, contrary to Dr. Hongo's opinion, the art does not recognize a reliable nexus between *in vitro* assays and *in vivo* treatment. In particular, characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tissue. For example, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation

on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Given the above, it is clear that *in vitro* cell culture assays cannot duplicate the complex conditions of *in vivo* environment. Further, in the assays, the therapeutic is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. Given the above, it is clear that the Hongo Declaration, although it demonstrates *in vitro* activity of particular monoclonal antibodies that appear to be specific for the receptor assayed, does not provide corroboration of the usefulness of the claimed invention.

Applicant further argues that the McNamara reference conclusion that trkC "may" be involved in pathologic morphologic rearrangements teaches one of ordinary skill in the art how to use the claimed invention. The argument has been considered but has not been found persuasive for the reasons of record. For the reasons of record one could not reliably predict that the invention would function as claimed. This point appears to be corroborated given that, as set forth above, a search of the literature, today, twelve years post filing did not reveal a single reference wherein a predictable nexus between NT-3, neuronal sprouting, trkC and treatment of epilepsy has been established.

Applicant argues that Hongo states that "Trk-specific antibodies...find use in the treatment of diseases characterized by ...Trk receptor expression as

determined by mRNA or protein assessments. These remarks were directed to treatment of diseases such as those discussed at page 4, lines 6-10 and page 68 lines 1829, e.g. aberrant neuronal sprouting at p. 68, lines 28-29. The argument has been considered but has not been found persuasive because the Hongo Declaration is not drawn to the treatment of epilepsy with antibody therapeutic. The data presented in the Hongo Declaration is not commensurate in scope with the claimed invention and Dr. Hongo's opinion, in the absence of objective evidence, is not convincing for the reasons set forth previously and above. Further, a review of the specification at page 4, lines 6-10 reveals that the specification teaches that the activities of neurotrophins "have led to interest in using neurotrophins as treatments of certain neurodegenerative diseases. Neurotrophins have also been implicated in the mediation of inflammatory pain, and are overexpressed in certain types of malignancies. Accordingly, inhibitors of neurotrophin biological activity have therapeutic potentials, such as in pain medication and as chemotherapeutics in cancer treatment." Clearly this teaching is not drawn to SEQ ID NO:6 or to the treatment of epilepsy. Further, a review of p. 68, reveals only that the specification teaches that antagonist activity against trk polypeptide (as defined broadly in the specification) is believed to be useful in the treatment of pathological conditions" such as "aberrant sprouting in epilepsy". For the reasons set forth previously and above, none of the specification as originally filed, the references or the Declaration provide enablement for the instantly claimed invention.

Applicant argues that the claims as amended are directed to aberrant neuronal sprouting in epilepsy, the treatment requiring contacting epileptic neuronal cells expressing full-length SEQ ID NO:6. Given this, the claims are

drawn to a specific population of patients and these patients would predictably benefit from the instantly claimed method. The argument has been considered but has not been found persuasive because the predictability of treatment of any population of patients has not been established for the reasons of record. Further, even if predictability of the treatment of epilepsy patients were to be established, the specification provides neither guidance nor information on how to predictably identify those patients that would benefit from the therapy, wherein the antagonism of full length SEQ IN NO:6 would predictably result in effective treatment of the disease.

Applicant argues that given the teachings of the specification, it would be expected that antagonistic antibodies would be useful and effective for the claimed treatment and points to pages 69-71 wherein guidance for treatments is to be found. The argument has been considered but has not been found persuasive because of the reasons set forth previously and set forth above. No one of skill would believe it more likely than not that the antagonistic antibodies would be useful or effective for the claimed treatment based on the single mention of aberrant neuronal sprouting and epilepsy in the specification at page 68, based on the teachings of the specification as originally filed or the art of record. In particular as drawn to the cited pages 69-71, a review of pages 69-71 of the specification reveals teachings drawn to storage and preparation of therapeutic formulations. The general teachings set forth do not enable the claimed invention.

The arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC 112

5. Claims 1, 4-7, 23 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a method for treating aberrant neuron sprouting in epilepsy....contacting a full-length human trkC receptor.....with antibody....." has no clear support in the specification and the claims as originally filed. Applicant argues that the new claim amendments are supported in the specification at page 68, lines 28-29 and in Figure 2B. The argument has been considered but has not been found persuasive because a review of page Figure 2B reveals a partial sequence of SEQ ID NO:6, apparently drawn to the tyrosine kinase domain which is identified by being enclosed in arrows. Further a review of page 68, lines 19-29 reveals the only mention of epilepsy or aberrant sprouting in the specification at lines 28-29. Although the specification teaches that trkC polypeptides of the present invention as well as the antibodies specifically binding such receptors are useful in blocking the biological activity of neurotrophins capable of binding these trk receptors and further teaches that "antagonist activity is believed to be useful in the treatment of pathological conditions" such as "aberrant sprouting in epilepsy", there is no teaching of an antagonist specific to the "full length TrkC receptor, SEQ ID NO:6. Further, a review of the specification reveals at paragraph 0057 of the published application that "the term "trk polypeptide" with or without an affixed capital letter (e.g., A, B or C) designating specific members within this family, specifically include "native" or "native sequence" receptors (wherein these terms are used interchangeably) from any animal species including full length receptors, their truncated and variant forms, such as those arising by alternate splicing and/or insertion, and naturally-

occurring allelic variants, as well as functional derivatives of such receptors." Given the above, given the broadly defined trkC receptor polypeptides, given the lack of guidance in the specification as to which of the whole universe of molecules encompassed by the definitions is intended to be useful for the treatment of aberrant sprouting in epilepsy, the suggested support is not found persuasive. The subject matter claimed in claims 1, 4-7, 23 broadens the scope of the invention as originally disclosed in the specification.

6. Claims 1, 4-7, 23 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a method for treating aberrant neuron sprouting in epilepsy....contacting..... receptor.....expressed in epileptic neuronal cells .....with antibody....." has no clear support in the specification and the claims as originally filed. Applicant argues that the new claim amendments are supported in the specification at page 68, lines 28-29 and in Figure 2B. The argument has been considered but has not been found persuasive because a review of page Figure 2B reveals a partial sequence of SEQ ID NO:6, apparently drawn to the tyrosine kinase domain which is identified by being enclosed in arrows. Further a review of page 68, lines 19-29 reveals the only mention of epilepsy or aberrant sprouting in the specification at lines 28-29. Neither citation is drawn to contacting an epileptic neuronal cell in the claimed method. A search of the specification reveals no teaching drawn to contacting epileptic neuronal cells for the claimed treatment. The subject matter claimed in claims 1, 4-7, 23 broadens the scope of the invention as originally disclosed in the specification.

7. Claims 23 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a

method for treating an epileptic condition comprising aberrant neuron sprouting" has no clear support in the specification and the claims as originally filed. Applicant argues that the new claim amendments are supported in the specification at page 68, lines 28-29 and in Figure 2B. The argument has been considered but has not been found persuasive because a review of page Figure 2B reveals a partial sequence of SEQ ID NO:6, apparently drawn to the tyrosine kinase domain which is identified by being enclosed in arrows. Further a review of page 68, lines 19-29 reveals the only mention of epilepsy or aberrant sprouting in the specification at lines 28-29. Neither citation is drawn to treating an epileptic condition comprising aberrant neuron sprouting. A search of the specification reveals no teaching drawn to treating an epileptic condition comprising aberrant neuron sprouting. It is suggested that Applicant review the paper mailed 3/28/2005, pages 4-5 wherein the heterogeneity of epileptic disorders is discussed, wherein more than 40 epileptic conditions are known. The subject matter claimed in claim 23 broadens the scope of the invention as originally disclosed in the specification.

8. All other objections and rejections recited in Paper No. 13 are withdrawn.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 5:30am to 2pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
April 4, 2006